Original Research Article

Studies on the pharmacokinetics of piperacillin/ tazobactam in renal replacement therapy in patients with chronic renal failure

Qinqin Ma*, Hongyuan Xiao, Yannan Zhang, Chen Chen, Ying Zhou, Yunning Liu, Tianmin Li, Yinghua Yu
The First Affiliated Hospital of Hebei North University, Intensive Care Unit, Hebei 075000, China

For correspondence: **Email: shoulibenci3270@163.com*

Abstract

Purpose: To study the pharmacokinetics of piperacillin/tazobactam in renal replacement therapy (CRRT) in patients with chronic renal failure (CRF).

Methods: Six CRF patients treated with CRRT in the First Affiliated Hospital of Hebei North University from April 2020 to July 2020 were selected and administered 4 g of piperacillin and 0.5 g of tazobactam within 30 min after, and at 5, 30, 45, 60, 90, 120, 180, 240, 360 and 480 min after CRRT. The DAS software was used to calculate pharmacokinetic parameters while linear regression was used to analyze the relationship among patient characteristics, CRRT parameters, and pharmacokinetics.

Results: The C_{max} of piperacillin and tazobactam was 118.46 (96.12 - 161.12) mg/L and 27.45 (14.75 - 28.45) mg/L, while the volume of distribution (V_d) was 1.16 (0.72 - 1.59) L/h and 0.72 (0.57 -0.82) L/kg, respectively. The value for elimination half-life ($t_{1/2}$) was 4.66 (3.19 -8.45) h and 4.25 (3.42 - 5.96) h, while total clearance (CL) was 7.28 (5.58 - 9.73) L/h and 6.37 (4.28 - 10.04) L/h, respectively. Multivariate linear regression showed that piperacillin C_{max} was negatively correlated with the flow velocity of the substitution fluid (β = -0.679, 95 % CI = -0.278 - 0.943, p < 0.001). Piperacillin CL was positively correlated with the flow velocity of the waste liquid (β = 0.956, 95 % CI = 1.267 - 4.796, p < 0.001).

Conclusion: When used in CRF patients receiving CRRT, piperacillin and tazobactam show decrease in C_{max} and CL, but increase in $t_{1/2}$. This finding should provide useful guidance for clinicians concerned.

Keywords: Piperacillin/tazobactam, Chronic renal failure, Renal replacement therapy, Pharmacokinetics

INTRODUCTION

Chronic renal failure, the terminal stage of chronic kidney disease, presents with obvious renal atrophy, and impairment of body functions such as excretion, acid-base balance and body fluid maintenance. It is characterized by high incidence, severe complications, and poor prognosis [1,2]. The major objective of clinical treatment is to delay worsening of the disease and improve prognosis. Renal failure leads to hemodynamic instability. Continuous renal replacement therapy (CRRT) is a favorable treatment option for renal failure patients [3].

However, while CRRT removes body fluids and solutes, it also clears drugs from the body, resulting in an impact on the pharmacokinetics (PK)/pharmacodynamics (PD) of drugs. Piperacillin and tazobactam are drugs frequently used in the treatment of chronic renal failure. This study analyzed the pharmacokinetic characteristics of piperacillin and tazobactam in patients with chronic renal failure receiving CRRT, and investigated the associated influencing factors, with a view to providing a guide for clinical administration of these drugs.

METHODS

General information on patients

This is a prospective study. This study was approved by the Ethical Committee of the First Affiliated Hospital of Hebei North University (approved no. 2018KY283). This study was performed in accordance with principles of the Declaration of Helsinki [4]. All patients signed informed consent. Patients with chronic renal failure who received CRRT treatment in our hospital from April 2020 to July 2020 were included. The included patients were: ① patients with complete clinical data, aged 18 to 70 years; ② patients who met the diagnostic criteria for chronic renal failure (blood creatinine ≥ 26.5 μmol/L, and glomerular filtration rate < 60 ml/min); ③ patients who satisfied CRRT indications (poor diuretic response, severe electrolyte imbalance, etc.); ④ those who had not used drugs containing piperacillin and tazobactam within 2 weeks before CRRT, and ⑤ patients who were aware of the study objectives, and volunteered as participants. The exclusion criteria were: ① history of infection, major trauma, and surgery within 3 months before admission; ② use of anti-chronic renal failure drugs within 3 months before admission; ③ presence of parathyroid disease or malignant tumor; and ④ allergy to piperacillin or tazobactam. This study received approval from the ethics committee of our hospital.

Renal replacement therapy (CRRT)

The PRISMA continuous blood purification instrument and supporting pipelines and filters (area: 0.9 m^2; AN69HF hollow fiber; Sweden GAMBRO Medical Equipment Company) were applied. The mode adopted was uniform continuous venous-venous hemodiafiltration for more than 12 h. In accordance with the requirements of the guidelines, the prescribed dose of CRRT was set as the flow rate of the waste liquid ≥ 30 mL/kg/h, and the doctor in charge was at liberty to increase the prescribed dose in response to changes in patient's blood pressure, acid-base balance and electrolyte disorders.

Drug administration and specimen collection

The selected patients were subjected to instillation of piperacillin (4 g) and tazobactam (0.5 g) at a uniform rate within 30 min after the start of CRRT, and at 15, 30, 45, 60, 90, 120, 180, 240, 360, 480 min after the end of CRRT. Then, 5 mL of peripheral venous blood was drawn, and 2 mL of supernatant was taken after centrifugation and stored at -80 °C. Based on the patient's condition, other treatments were given e.g., use of combination of other drugs, but piperacillin and tazobactam were excluded from these combinations.

Chromatographic analysis

Agilent 1260 high-performance liquid analyzer produced (Agilent Inc.) was used to measure blood drug concentrations.

Chromatographic conditions for Piracillin

The column used was Agilent ZORBAX SB-C18 (4.6 mm × 150 mm, 5 μm in diameter), and the mobile phase was 0.025 mol/L sodium dihydrogen phosphate-acetonitrile (75:25, v:v).

Chromatographic conditions for tazobactam

The column used was Agilent ZORBAX SB-C18 (4.6 mm × 250 mm, 5 μm in diameter), with a mobile phase of 0.025 mol/L dihydrogen phosphate sodium-acetonitrile (90: 10, v:v).

Statistical analysis

Counting data are expressed as percentage (%), while measurement data are expressed as median or interquartile differences. The DAS software was used to calculate pharmacokinetic parameters. Spearman correlation coefficient (r) and linear regression were employed to determine the relationship between patient characteristics and CRRT parameters and pharmacokinetic results. All statistical analyses were done with SPSS 19.0 software. Differences were deemed statistically significant at $p < 0.05$.

RESULTS

Patient profile

A total of 6 patients were enrolled (4 males and 2 females); 66 blood samples were collected, and their drug concentrations were measured. Before

CRRT, there were 3 cases of stage III, 2 cases of stage IV, and 1 case of stage V chronic renal failure. Two (2) patients received norepinephrine at a dose of 0.5 µg/kg/min), 3 patients received dopamine at a dose of 8 µg/kg/min), while 1 patient received norepinephrine and dobutamine (norepinephrine dose: 0.2 µg/kg/min; dobutamine dose: 5 µg/kg/min). The general information on the patients on admission is shown in Table 1.

CRRT parameters of patients

All patients used the dilution method before CRRT, and 3 patients took high-dose prescriptions due to severe acid-base imbalance (2500 mL/h for substitution fluid, 2000 mL/h for dialysate, and total waste flow velocity of 75 mL/kg/h). The other 3 patients were treated with unfractionated heparin for anticoagulation. The specific CRRT parameters are shown in Table 2.

Pharmacokinetic parameters of piperacillin/ tazobactam

The peak concentrations (C_{max}) of piperacillin and tazobactam were 118.46 (range = 96.12 - 161.12) mg/L and 27.45 (range = 14.75 - 28.45) mg/L, respectively, while the values of volume of distribution (V_d) were 1.16 (range = 0.72 - 1.59) and 0.72 (range = 0.57 - 0.82) L/kg, respectively.

Their elimination half-life ($t_{1/2}$) values were 4.66 (3.19 - 8.45) and 4.25 (3.42 - 5.96) h, while total clearance (CL) values were 7.28 (range = 5.58 - 9.73) and 6.37 (range = 4.28 - 10.04) L/h, respectively. These results are shown on Table 3. The blood concentration curves of piperacillin and tazobactam are shown in Figure 1 and Figure 2.

Correlation analysis of piperacillin pharmacokinetic parameters with patient characteristics and CRRT parameters

The correlations of pharmacokinetic parameters of piperacillin (C_{max}, AUC, $t_{1/2}$, CL) with patient's APACHE II score, stage, creatinine, albumin, hematocrit, substitution fluid flow velocity, dialysate flow velocity, blood flow velocity, flow velocity of waste liquid, urine output during the observation period, and liquid balance were analyzed using Spearman correlation analysis. The results showed that C_{max} was correlated with substitution fluid flow velocity, dialysate flow velocity, waste fluid flow velocity, and urine volume ($p < 0.001$). Moreover, AUC was correlated with dialysate flow velocity and urine volume ($p < 0.001$); $t_{1/2}$ and waste fluid flow velocity were correlated ($p < 0.001$), while CL was correlated with dialysate flow velocity and waste fluid flow velocity ($p < 0.001$).

Table 1: General information on patients on admission

Gender	Age (years)	APACHEII (points)	Chronic renal failure	Serum creatinine (µmol/L)	Albumin (g/L)	Hematocrit value (%)
Male	49	21	Stage III	495.13	23.56	17.53
Male	66	24	Stage IV	532.67	15.72	19.41
Female	65	26	Stage V	625.78	10.19	14.51
Male	29	19	Stage III	506.14	22.85	26.26
Female	61	20	Stage IV	480.35	19.21	18.13
Male	56	22	Stage III	432.29	23.58	20.52

Table 2: CRRT parameter settings for patients

| *AC	LMWH	UFH	UFH	LMWH	UFH	LMWH
Before administration (h)	1.0	1.5	1.5	0.5	1.5	1.0
Substitution fluid flow velocity (L/h)	2.0	1.5	2.5	1.5	2.0	2.0
Dialysate flow velocity (L/h)	1.0	1.0	1.5	1.0	1.0	1.5
Blood flow velocity (mL/min)	200	180	150	180	180	180
waste fluid flow velocity (mL/kg/h)	75	69	63	74	71	66
CRRT fluid balance (mL)	600	800	-100	550	400	1000
CRRT urine volume (mL)	150	60	80	200	120	180

*AC = anticoagulant; LMWH = high-dose prescription anticoagulant; UFH = unfractionated heparin anticoagulant

Table 3: Pharmacokinetic parameters of piperacillin and tazobactam [median (upper limit - lower limit)]

Pharmacokinetic parameter	Piperacillin	Tazobactam
C_{max} (mg/L)	118.46 (96.12-161.12)	27.45 (14.75-28.45)
AUC (0-6) (mg·L^{-1}·h^{-1})	379.45 (294.17-423.18)	62.17 (40.38-78.26)
V_d (L/kg)	1.16 (0.72-1.59)	0.72 (0.57-0.82)
$t_{1/2}$ (h)	4.66 (3.19-8.45)	4.25 (3.42-5.96)
CL (L/h)	7.28 (5.58-9.73)	6.37 (4.28-10.04)
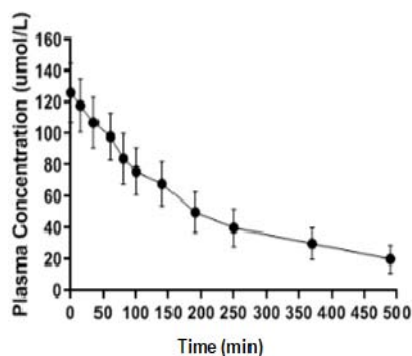
Figure 1: Changes in the plasma concentration of piperacillin over time
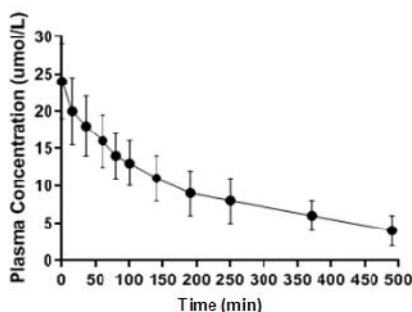
Figure 2: Changes in the plasma concentration of tazobactam with time

The pharmacokinetic results and the respective related factors were subjected to a multivariate linear regression, and the results indicated that piperacillin C_{max} was significantly negatively correlated with the flow velocity of the substitution fluid (β = -0.679, 95 % CI = -0.278 - 0.943, p < 0.001, Table 4). Moreover, piperacillin CL was significantly positively correlated with the flow velocity of waste liquid (β = 0.956, 95 % CI = 1.267 - 4.796, p < 0.001). These results are shown in Table 5.

DISCUSSION

Chronic renal failure patients may experience systemic damage as time goes on until terminal stage of renal failure which requires CRRT treatment [5-10]. The disease causes a series of adverse drug reactions. It may be that CRRT removes drugs from the body when it clears body fluids and solutes, leading to poor drug effects and some adverse drug reactions [11-13]. For this reason, research on human pharmacokinetics of renal replacement therapy in patients with chronic renal failure can provide true and accurate pharmacokinetic data for evaluation of the performance of pharmaceutical preparations. Moreover, it will help to determine the necessity, research methods, and subsequent administration of large-scale clinical trials.

In this study, a prospective analysis was conducted on the first dose of piperacillin/tazobactam (4.5 g) in patients with chronic renal failure treated with CRRT. Under normal circumstances, the evaluation of pharmacodynamics of an antibiotic is carried out after 4 to 5 administration cycles, since the drug would have attained a stable level in the blood by that time [14]. However, for patients with chronic renal failure, it is hoped that the pharmacodynamic indicators can be reached quickly after administration, so as to delay the patient's disease deterioration early and improve prognosis. Usually, in patients receiving CRRT, drug clearance is not only affected by physiological renal clearance, but also by the external CRRT clearance.

With advances in CRRT, it is now known that many factors such as coagulation in the filter, fibrin adhesion to the filter, and polarization effect may reduce the clearance efficiency of CRRT [15]. In contrast, the clearance changes with improvement or deterioration of kidney function. Therefore, analysis of pharmacokinetics within 8 h of the first dose after CRRT treatment can reduce the effects of changes in renal function and filter status on pharmacokinetics after multiple doses.

Table 4: Multivariate linear regression analysis of C_{max} in the pharmacokinetic parameters of piperacillin

Factor	β	SE	Waldχ²	P-value	OR (95% CI)
Substitution fluid flow velocity	-0.679	0.178	-7.629	0.001	0.507 (-0.278~0.943)

Table 5: Multivariate linear regression analysis of CL in the pharmacokinetic parameters of piperacillin

Factor	β	SE	Waldχ²	P-value	OR (95%CI)
Waste fluid flow velocity	0.956	0.394	5.887	0.001	2.601(1.267~4.796)

The median plasma peak concentrations C_{max} of the first doses of piperacillin (4 g) and tazobactam (0.5 g) for patients with chronic renal failure treated with CRRT were 118.46 (96.12 - 161.12) mg/L and 27.45 (14.75 - 28.45) mg/L, respectively, and they were negatively correlated with the flow velocity of the substitution fluid (β = -0.679, 95% CI = -0.278 - 0.943, p < 0.001). The peak plasma concentration was significantly lower than the 298 and 34 mg/L indicated in the drug insert, suggesting that CRRT affected the peak plasma concentrations of piperacillin and tazobactam [16,17]. The increase in volume of distribution (V_d) may be responsible for the significant decrease in peak plasma concentration, since the increase in V_d is common in critically ill patients. In this study, the V_d values of piperacillin and tazobactam were 1.16 (0.72 - 1.59) L/kg and 0.72 (0.57 -0.82) L/kg, respectively. These values are markedly higher than those obtained earlier in a study on healthy volunteers [17].

Elevated V_d is closely related to fluid resuscitation, hypoproteinemia and vascular endothelial injury. The elimination of piperacillin and tazobactam from the body depends mainly on the kidneys. About 68 % piperacillin and 80 % tazobactam are excreted through the kidneys in their original drug forms. Theoretically, glomerular filtration rate can be used as an index of the amount of drug eliminated from the body. However, there is no good method for evaluating the degree of abnormality in renal filtration in patients with chronic renal failure. Indeed, serum creatinine and urine output, which are widely used in chronic kidney disease, cannot accurately reflect renal filtration [18]. The molecular mass of piperacillin is 517.6, while that of tazobactam is 300.3. Both are small molecules which, in theory, are easily removed through CRRT. However, in practice, the clearance rate differs with different filters, modes, and dose regimens.

The present study adopted a unified filter and mode to avoid the influence of different filters and modes on the clearance of the drugs. The usage time of the filter is controlled in a relatively narrow range (1.0 - 1.5 h) to avoid compromising the efficiency of filtration. The results of this study showed that the total clearance of piperacillin and tazobactam were 7.28 (5.58 - 9.73) and 6.37 (4.28 - 10.04) L/h, respectively, and they were significantly positively correlated with the dialysate flow velocity (β = 0.956, 95 % CI = 1.267 - 4.796, p < 0.001). The amount of waste fluid in CRRT is the sum of total fluid volume from dialysis, replacement and dehydration, and it has been proven to be a dose indicator for CRRT [19]. Piperacillin is a first-class elimination kinetics drug. The decrease in clearance rate and the increase in volume of distribution prolong $t_{1/2}$. Tazobactam serves to inhibit bacterial β-lactamase and enhance the antibacterial activity of piperacillin, and its $t_{1/2}$ is involved in a coordinated role with that of piperacillin [20].

Limitations of the study

First, the sample size of the study is small, which may not truly reveal the pharmacokinetics of piperacillin/tazobactam during CRRT; in addition, it is a common practice to evaluate the pharmacodynamics based on the blood drug concentration. However, in patients with sepsis, the tissue (target organ) concentration of the drug may be much lower than the blood concentration, and the pharmacodynamic index calculated based on the blood concentration may overestimate the bactericidal effect.

CONCLUSION

When used in chronic renal failure patients receiving CRRT, piperacillin and tazobactam significantly decrease C_{max}, increase $t_{1/2}$, and decrease CL. Since the cases in this study were only from one hospital, and the sample size is limited, the results may be biased. Thus, larger samples and multi-center studies are needed to enhance the reliability of the results.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

REFERENCES

1. Shigematsu T, Muraoka R, Sugimoto T, Nishizawa Y. Risedronate therapy in patients with mild-to-moderate chronic kidney disease with osteoporosis: post-hoc analysis of data from the risedronate phase III clinical trials. BMC Nephrol 2017; 18: 66.
2. Pinto AR, da Silva NC, Pinato L. Analyses of melatonin, cytokines, and sleep in chronic renal failure. Sleep Breath 2016; 20: 339-344.
3. Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, Chen M, He Q, Liao Y, Yu X, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet 2012; 379: 815-822.
4. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013; 310: 2191-2194.
5. Turgutalp K, Kıykım A, Bardak S, Demir S, Karabulut Ü, Özcan T, Helvacı I, Gözükara Y. Is the red cell distribution width strong predictor for treatment response in primary glomerulonephritides? Ren Fail 2014; 36: 1083-1089.
6. Shah BV, Patel ZM. Role of low protein diet in management of different stages of chronic kidney disease - practical aspects. BMC Nephrol 2016; 17: 156.
7. Rizzetto F, Leal VO, Bastos LS, Fouque D, Mafra D. Chronic kidney disease progression: a retrospective analysis of 3-year adherence to a low protein diet. Ren Fail 2017; 39: 357-362.
8. Bellizzi V, Cupisti A, Locatelli F, Bolasco P, Brunori G, Cancarini G, Caria S, De Nicola L, Di Iorio BR, Di Micco L, et al. Low-protein diets for chronic kidney disease patients: the Italian experience. BMC Nephrol 2016; 17: 77-77.
9. Ko GJ, Obi Y, Tortorici AR, Kalantar-Zadeh K. Dietary protein intake and chronic kidney disease. Curr Opin Clin Nutr Metab Care 2017; 20: 77-85.
10. Hekmat R, Maghsudloo F, Mohebi M, Rezaee SA, Vakili R, Panah HR. A study of the main determinants of sexual dysfunction in women aged 15-45 years on

11. chronic hemodialysis. Saudi J Kidney Dis Transpl 2016; 27: 916-920.
11. Al-Biltagi M, Tolba OA, ElHafez MA, Abo-Elezz AA, El Kady EK, Hazza SM. Oxidative stress and cardiac dysfunction in children with chronic renal failure on regular hemodialysis. Pediatr Nephrol 2016; 31: 1329-1339.
12. Zahed NS, Ghassami M, Nikbakht H. Effects of coenzyme Q10 supplementation on C-reactive protein and homocysteine as the inflammatory markers in hemodialysis patients; a randomized clinical trial. J Nephropathol 2016; 5: 38-43.
13. Johnson DW, Atai E, Chan M, Phoon RK, Scott C, Toussaint ND, Turner GL, Usherwood T, Wiggins KJ; KHA-CARI. KHA-CARI guideline: Early chronic kidney disease: detection, prevention and management. Nephrology 2013; 18: 340-350.
14. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006; 34: 1589-1596.
15. Fayad AI, Buamscha DG, Ciapponi A. Intensity of continuous renal replacement therapy for acute kidney injury. Cochrane Database Syst Rev 2016; 10: CD010613- CD010613.
16. Varghese JM, Jarrett P, Boots RJ, Kirkpatrick CM, Lipman J, Roberts JA. Pharmacokinetics of piperacillin and tazobactam in plasma and subcutaneous interstitial fluid in critically ill patients receiving continuous venovenous haemodiafiltration. Int J Antimicrob Agents 2014; 43(4): 343-348.
17. Bauer SR, Salem C, Connor MJ Jr, Groszek J, Taylor ME, Wei P, Tolwani AJ, Fissell WH. Pharmacokinetics and pharmacodynamics of piperacillin-tazobactam in 42 patients treated with concomitant CRRT. Clin J Am Soc Nephrol 2012; 7: 452-457.
18. Bragadottir G, Redfors B, Ricksten SE. Assessing glomerular filtration rate (GFR) in critically ill patients with acute kidney injury--true GFR versus urinary creatinine clearance and estimating equations. Crit Care 2013; 17: R108-R108.
19. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012; 120: c179-c184.
20. Liu Q, Rand K, Derendorf H. Impact of tazobactam pharmacokinetics on the antimicrobial effect of piperacillin-tazobactam combinations. Int J Antimicrob Agents 2004; 23: 494-497.